2017

Meta-analysis of studies on CPR: a better route to new practice guidelines

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Abstract

Quantitative synthesis of research results multiple small clinical trials using the statistical techniques of meta-analysis yields conclusions in excellent agreement with large randomized "mega-trails". The present paper introduces a simple yet powerful method of meta-analysis for combining results of any published studies of a proposed treatment compared with a suitable control. These may include pre-clinical or clinical models generating either continuous or dichotomous data.

Introduction

Many promising refinements in emergency cardiovascular care are based upon limited research studies conducted by an under-funded community of scientists who are largely unsupported by multinational corporations or federal grants. In this research domain multiple large clinical trials on the same topic are scarce. This situation forces practice guideline writers to make the most efficient use of available data, typically from under-powered studies, to somehow combine, weigh, and sum data from a diverse clinical and animal models. Traditional narrative reviews, taking note of the proportion of individual studies with statistically significant results, often lead to false negative conclusions and unnecessary delays in the clinical use of research findings[1-3].

In many fields of medicine statistical methods of meta-analysis are now used to combine research from multiple small studies in order to obtain greater effective power (i.e. the ability to detect true positive effects) similar to that of a single large study or "mega-trial". Recently, however, the utility of meta-analysis has been called into question by reports that about 20 percent of published meta-analyses of multiple small trials have been subsequently contradicted by results of large trials, which were interpreted as a "gold standard"[4,5,6]. Here "contradicted" means that the 95 percent confidence interval for one, but not the other, excluded the null hypothesis. (In no case was there a treatment effect significant in one direction in a meta-analysis and significant in the opposite direction in a mega-trial.) The finding of 20 percent disagreement is actually quite reasonable when one realizes that we do not know for certain whether the treatment under study actually produces a positive, negative,

or null effect. Both the meta-analysis and the putative gold standard mega-trial are subject to random sampling error, depending on their power. Either or both could have false positive or false negative results.

Suppose, for example, that one half of all effects studied are actually positive and the other half of effects are only apparent, i.e. the null hypothesis is true, in keeping with published reviews of many meta-analyses[5,7]. First consider only the treatments with actual positive effects. Suppose that the power of the gold standard mega-trial is 80 percent, as was true in the studies of Villar et al. [4] and of Cappelleri et al.[6], and that the power of the meta-analysis of small trials is also 80 percent. Both will give true positive results 64% of the time (0.8 x 0.8). Both will give false positive results 4% of the time (0.2 x 0.2). Hence the two will agree 68% of the time and disagree 32% of the time. Now, consider only the treatments with actual null effects, that is, for which the null hypothesis is true. Suppose the p=0.05 cutoff is used for two-tailed tests of significance. If a "negative" result is defined as no significant positive effect of the experimental treatment, then both the small studies and the mega-trial will indicate true negative results 95.06% of the time (0.975 x 0.975). Both will indicate false positive results 0.06% of the time (0.025 x 0.025). Hence the two will agree 95.12% of the time and disagree 4.88% of the time. If half of all effects are actually positive and half are null, then the expected overall agreement rate will be 82%, and the disagreement rate will be 18 percent.

This simple calculation is quite close to the observed agreements of 80% reported by Villar[4], 80% reported in a separate study by LeLorier et al.[5], and 82% reported by Cappelleri et al.[6] for "gold standard" mega-trials with 80% power. Hence the observed agreement rate between meta-analyses of series of small studies and subsequent large studies is almost exactly as one would expect if the two approaches were measuring the same phenomena in an equally valid way. Thus, meta-analysis is as useful as a similarly powered mega-trail in predicting the existence of a true treatment effect. This conclusion appears to be true despite often raised objections to meta-analysis[3,8] on the basis that one "shouldn't combine apples and oranges" either in terms of patient populations, experimental designs or models, end points examined, or perceived quality of research methods.

Methods and Results

As described in detail elsewhere[12], the author has developed a simple and easily implemented technique of meta-analysis designed specifically as an aid to evidence evaluation in the creation of practice guidelines for emergency cardiovascular care[**]. This method is immune from the systematic and excessive Type II errors associated with the traditional "vote-counting" methods of research synthesis[1-3]. It is designed to demystify meta-analysis and to place control of the technical aspects of the process directly in the hands of clinical decision-makers. Any studies that compare a new method (drug, dose, or device) with a standard or control method can be weighed and summed. Examples include interposed abdominal compression-CPR versus standard CPR, vasopressin versus epinephrine in cardiac arrest, or pre-hospital basic life support with and without use of automatic external defibrillators.

[**] An electronic copy of a spreadsheet for performing a meta-analysis is available free of charge from the author--email babbs@purdue.edu.

Outcome measures need not be directly comparable. Some end points may be continuous data (physiologic measures like end-tidal CO_2 or mean coronary perfusion pressure). Other end points may be dichotomous or binary data (integer head counts of patients resuscitated, surviving 24 hours, discharged, etc.). It is only necessary that all of the studies relate to a common theme or focused question.

The actual calculations require no more than a one-page spreadsheet. They are based upon elementary principles of statistics that can be validated by most physicians. A specialized statistical software package is not required. It is a straightforward task to make or borrow a sample spreadsheet of this type and then for each reviewed topic enter the required data. For continuous variables these include only experimental and control means and the corresponding standard errors and N's. For dichotomous variables the required data include only the numbers of patients with each recorded outcome in each group.

The first step of the meta-analysis is to quantify the findings of each relevant study in terms of dimensionless ratios of the measured results for the experimental group divided by the measured results for the control group. (This ratio is analogous to the relative risk used to describe negative outcomes in epidemiology.) The result ratios from multiple studies are then combined as a weighted average. The reviewer may assign weights based upon the type, design, level or evidence, or quality of each study. For example, Level 1 studies as described by Cummins and coworkers[9] (the highest level) could be assigned weight 1, and Level 2 studies (the next highest level) could be assigned weight 1/2, etc. The average result ratio and its 95% confidence interval are plotted to provide direct visual interpretation of the results. Under the null hypothesis the confidence interval of the average result ratio will usually overlap 1.00. These statistics can be re-computed after publication of each successive study in the series to provide a cumulative meta-analysis as described by Lau and coworkers[10,11]. Full technical details of the calculations are provided elsewhere[12].

Figure 1 is an example of a cumulative meta-analysis plot of the aggregate result ratios, r*, and their 95% confidence intervals with publication of successive human clinical trials of interposed abdominal compression CPR compared to standard CPR. The top data point and its 95 percent confidence interval represent the historically first trial, the second a combination of the first two trials, the third a combination of the first three, etc. Cumulative meta-analysis shows that a significant aggregate effect of treatment in humans is achieved after the publication of the fourth study. The lower 95 percent confidence limit for r* in all 5 studies is 1.22. Hence, if biological significance is defined as a 10 percent or greater improvement in results, the effect of IAC-CPR is likely to be biologically as well as statistically significant.

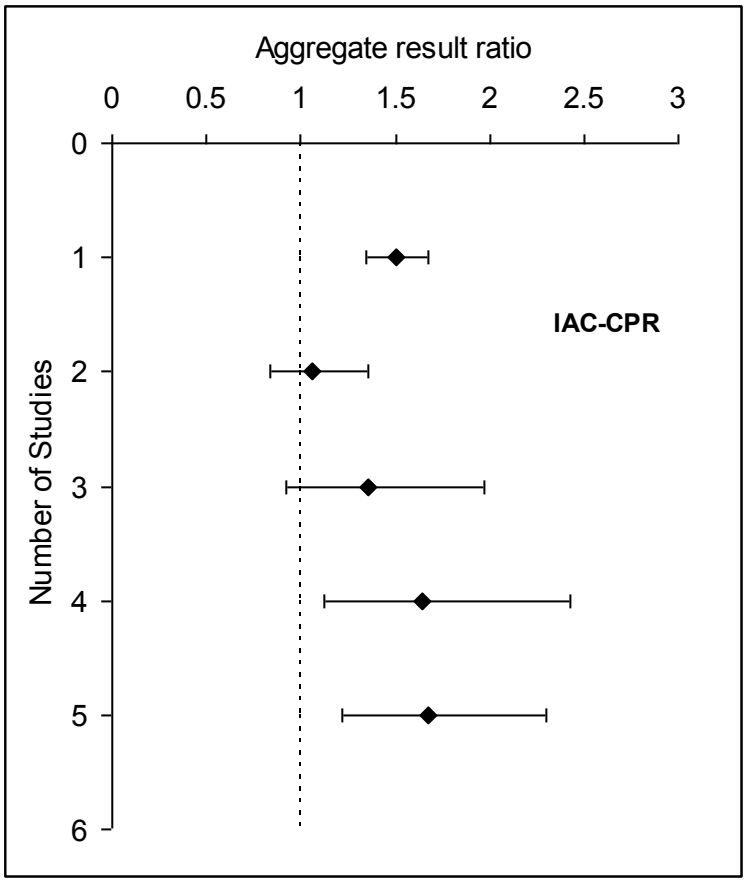

Figure 1. Cumulative meta-analysis of human clinical studies of interposed abdominal compression CPR. The studies in chronological order are cited in references [15], [16], [17], [18], [19]. Error bars represent 95 percent confidence intervals. The vertical line indicates results consistent with the null hypothesis. Weights were 0.5 for study #1 (small non-randomized, "Level 2"[9] trial) and 1.0 for all other studies (randomized, "Level 1" trials).

Discussion

Like individual trails, meta-analyses can be subject to bias. Selection of studies included in the meta-analysis depends greatly upon the viewpoint of the meta-analyst and the framing of the question to be addressed. Selection also may depend on subjective ratings of study quality, which can vary greatly[13]. Language bias may exclude trials published in languages other than English[14]. Sometimes data can be double counted inadvertently, for example in a separate single-center report of some of the same patients included in a multi-center trial. Studies with non-significant results -- especially ones with small sample size -- may be less

likely to be published (publication bias), and hence may not be accounted in a formal meta-analysis[14].

There are similar biases in mega-trials. The target population and implementation of the intervention are highly focused and necessarily exclusive. Certain countries, cultures, and languages are undoubtedly excluded. Some compromises in study sophistication or "quality" must necessarily be made to recruit adequate numbers of participating centers and patients. Inadvertent errors in data counts sometimes occur, and some off study uses of the intervention may go unreported. Perhaps, then, it should not be surprising that results of mega-trials and meta-analyses of smaller studies of the same intervention agree as much as can be expected on a statistical basis.

Conclusion

In the field of resuscitation meta-analysis can provide accurate and timely estimates of the amount of benefit or harm from an experimental intervention, minimizing the time between research discoveries and their clinical implementation.

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